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Mapping of the Cyclodextrin Cavity Using the Cylindrical Coordinate System

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(Received June 3, 2005; Accepted August 31, 2005)

This paper describes the mapping of the inner cavity of cyclodextrin and the guest molecule using the cylindrical coordinate system. Each cavity structure of α-, β-, and γ-cyclodextrin was examined using the coordinate system, in which, the Z-axis passes through the molecular axis; a normal of the plane that consists of 6, 7, or 8 C_1 atoms of glucose units was obtained using the least-squares methods and that passes through the center of C_1 atoms. The radius ρ is the distance from the Z-axis to the solvent-accessible surface of a cavity. The ϕ-axis is defined such that the nearest C_1 atom of the glucose unit to the Z-axis is its origin. The atomic character of the inner surface of the cavity was also obtained and plotted in the same coordinates. The guest molecule was plotted with the same coordinate system as cyclodextrin to see atoms with large ρ distance of the guest molecule on the solvent-accessible surface map of cyclodextrin. It was confirmed from the map that cyclodextrin molecules have an ellipsoidal shape, have pseudo-n-hold symmetry (n=6 to α, 7 to β, and 8 to γ) in relation to their molecular axis, and guest molecules are located in relatively hydrophobic regions. It was also confirmed that the maps of this system give insights into the complementary characters of structures between the host and the guest by plotting the guest molecule in the same coordinate system.

Key words——cyclodextrin; cylindrical coordinate; structure; mapping; cavity

INTRODUCTION

Almost all applications of cyclodextrins (CDs) involve complexation. CDs are not only molecular capsule reagents in analytical chemistry, but also their use extends to chiral recognition,[1] poorly soluble drugs, rapidly deteriorating flavors, toxic pesticides or dangerous explosives, and gases such as radioactive iodine molecules. By encapusulation of compounds in CDs, various advantages are obtained.[2,3] In 1995, more than a half-dozen companies worldwide were producing CDs, and their total output was in excess of 1000 tons/year. The price of β-CD is only several dollars per kilogram.[4]

Numerous X-ray structural analyses of α-, β-, and γ-CDs have been carried out and the results deposited in the Cambridge Structural Database (CSD).[5] The structures were summarized in detail by Saenger's group.[6] The structural aspects and physicochemical characters of CDs and guest molecules have also been studied intensively by computational chemistry, as reviewed previously.[7] Studies on the inclusion stability of many compounds have also been performed.[8—10] Ultrafast (nanosecond to picosecond) guest dynamics in the physical chemistry of CDs were reviewed by Douhal.[11]

Figure 1 shows the ball and stick representation of α-, β-, and γ-CD with each respective guest molecule drawn with RasTop 1–3.[12] The atom names of the glucose unit used are shown in Fig. 2. The unit number n in this study is 6 to 8.

In the introductory remarks in a paper on CDs in 1998, Szejtli reported the structural features of each CD such as the shape, cavity width, and cavity volume.[4]

Seanger et al.[6] reported that the structures of glucose 6 membered-rings of CDs are fairly rigid with a $^4C_1$ chair conformation and the only conformational freedom of the macrocycle resides in the rotation of the C_6-O_6 groups and rotational movement about the glucosidic link $C_1(n)$–$O_1(n\text{-}1)$–$C_4(n\text{-}1)$. They also pointed out that one of the important features of CDs concerns the distribution of hydrophobic and hydrophilic groups and that the hydrophilic hydroxyl groups occupy both rims of the cone and the inside of the cavity, although it is hydrophobic in character since it is covered by C_3–H, C_5–H, and C_6–H_2 and by the ether-like oxygen O_1, which constitutes a hydrophobic matrix in aqueous solution. They also

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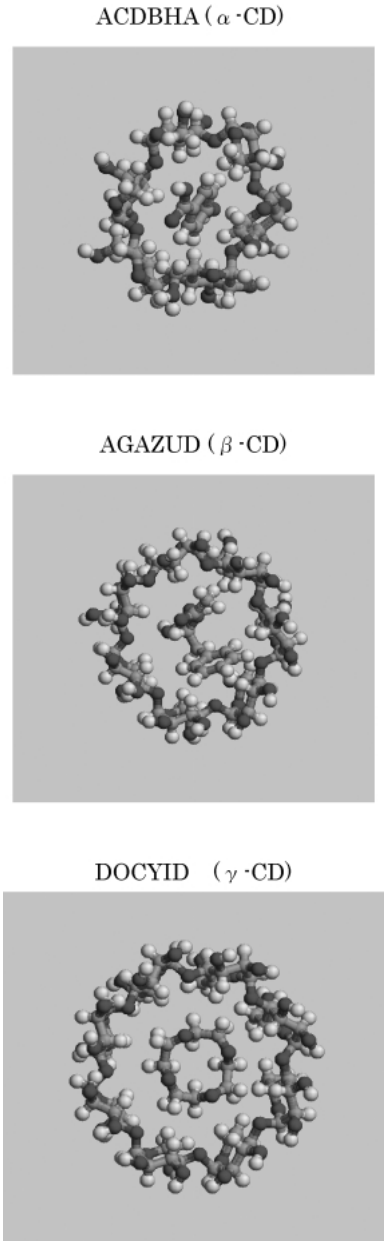

Fig. 1. Molecular Structure of α-, β-, and γ-CD

The entry codes are ACDHBA, AGAZUD, and DOCYID, respectively in the CSD. The guest molecule of CD is involved in each X-ray structural research and both the host and the guest molecules were used for the calculation throughout in this manuscript.

reported that the guest has little or no influence on the conformation of the glucose unit but may slighty distort the maclocycle of the enclosing CD upon complex formation.[6] Steiner and Saenger showed the importance of the structure not only of O–H···O hydrogen bonding but also of C–H···O hydrogen bonding between two adjacent glucose units,[13] which participate in maintaining the structure of the macrocycle. Harata pointed out the importance of hydrogen bonds between O_2–H and O_3'–H of adjacent glucose

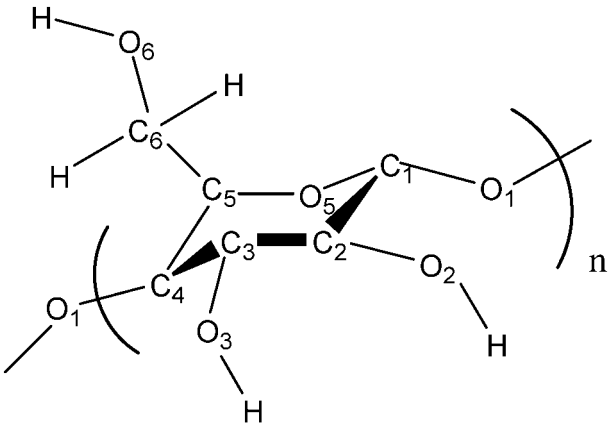

Fig. 2. Atom Names of the Glucose Unit of CD Used

units for macrocycle structure formation.[1] Lipkowitz pointed out that the conformation with the *n*-fold symmetry of CDs is not the most stable; symmetry breaking from an exact *n*-fold lowers the energies of those structures by large number of calculation using molecular mechanics.[7]

In NMR studies, the included part of the guest in CD gave rise to high-field chemical shifts while parts protruding from the CD interior demonstrated low-field shifts; these characteristic displacement features could be used to infer the orientation and penetration of the guest in the cavity. The 2-dimensional cross section of the cavity of CD along the molecular axis was usually used for structure determination in NMR studies.[14]

Lichtenthaler and Immel reported cavity mapping using the slice method containing the molecular axis of host molecules by exhibition of the actual 3-dimensional molecular structure.[15] They showed the inner surface radii of both rims, but could not show the surface structure and its roughness inside the cavity. For permethylated β-CD, Lipkowitz et al. found the most enantio-differentiating region of CD for chiral recognition and made contour plots.[16] Their contour plot method is also based on the exhibition of the actual 3-dimensional structure by the method of perspective drawing.

In this paper, the mapping of the cavity was carried out to obtain information on the solvent-accessible surface inside CD. The cylindrical coordinate system is convenient because a CD molecule has a shape resembling a deep dish.

The Z-axis coincides with the molecular pseudosymmetry axis, radius ρ is the distance from the Z-axis to the solvent accessible-surface (the value of ad-

dition atomic radii and probe radii 1.4 Å) of atoms which constitutes a cavity, and angle ϕ extends from 0° to 360°, the origin of which is from a normal of the Z-axis to the nearest C_1 atom. The cylindrical coordinate system used here is schematically shown in Fig. 3.

Mapping using the coordinate system yielded important information on the cavity structure of CD, that is, on the inner surface radius ρ and its roughness, and properties of CD where a guest molecule is in contact. Both maps are complementary. The guest molecules are also plotted on the same coordinate system for confirmation and to obtain visually structural information such as the importance of the hydrophobic character on inclusion and induced fitting to the structure of CDs.

METHODS

The crystal coordinates were first transformed into Cartesian coordinates. The crystallographic coordinates used for this calculation were from X-ray analyses from the CSD and hydrogen coordinates were generated by a program developed here. When a guest molecule was located far from the center of CD, the crystallographic symmetry operation was carried out to move the guest near the center of CD. In this study, no structural optimization was carried out. The plane composed of C_1 atoms was calculated using the least-squares method.

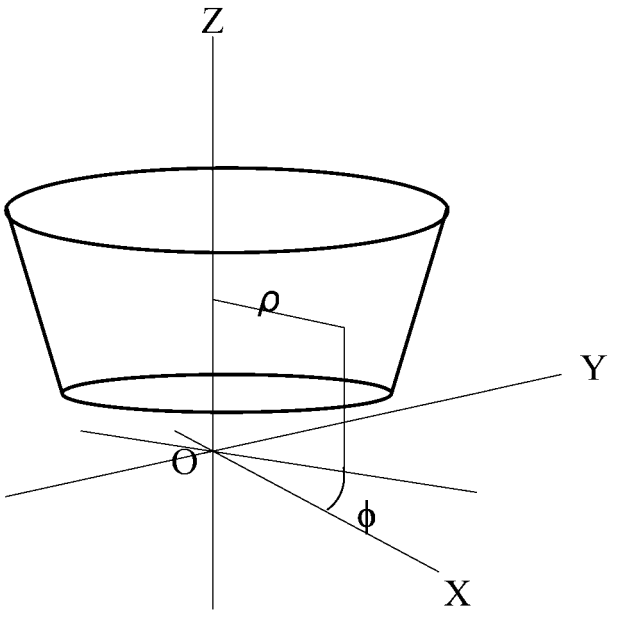

Fig. 3. Cylindrical Coordinate System Used and the Schematic Model of CD shown as a Cone

The first step of the calculation was the finding the plane equation of C_1 atoms (α-, β-, and γ-CD has 6, 7, and 8 C_1 atoms, respectively) and the direction of the plane normal was assigned to the Z-axis that passes through the center of C_1 atoms. The origin of the Z-axis was defined as the position at −4.0 Å apart from the small rim of a cone of CD (in stricter terms, the −4.0 Å position of the smallest Z-value atom). The C_1 atom nearest to the center of the C_1 atom ring was assigned to the X-axis direction in Cartesian coordinates. The vertical of the X-, and Z-axes was assigned to the Y-axis to give a righthand sense. Using direction cosines of new axes, the Cartesian coordinates in Å units from the crystallographic axes were transformed.

The mapping was performed as follows. The distance increment for the search for radius ρ was adopted as 0.02 Å, Z-axis increment was 0.1 Å and the angle increment was 2.0°. The solvent-accessible surface radius of the H-atom was taken as 2.4 Å, that of O as 2.8 Å, and that of C was 2.9 Å, which correspond to the magnitude of the addition of each atomic radius and probe radius (1.4 Å). When the distance from the Z-axis was increased, the coordinate became within the range of these solvent-accessible surface radii and then the distance was adopted as radius ρ of the cylindrical coordinate system. The calculation was carried out so that ϕ is from 0° to 360° and Z is increased until it was greater than the height of molecules along the Z-axis. As a result, the ellipsoidal structure of CD can be seen when ϕ is changed from 0° to 360° while the Z-value is kept constant. The inner-surface atomic species discriminating the H of O–H from that of C–H and ether oxygen from hydroxyl oxygen were also examined. The guest molecules were plotted on the same coordinate system to be able to visualize the outer atoms of a guest molecule on the solvent-accessible surface of the cavity of CD.

RESULTS

The results of CD mapping are shown in Figs. 4 through 9. The structures used here are from the CSD with entry codes ACDHBA,[17] AGAZUD,[18] and DOCYID.[19] Figures 4 and 5 are the results for α-CD, Figs. 6 and 7 are for β-CD and Figs. 8 and 9 are for γ-CD. In Figs. 4, 6, and 8, the cavity radius ρ of CD was mapped in the cylindrical coordinates, and the horizontal axis is the Z-axis and the vertical axis is the angle ϕ. Molecules were aligned to give the O_6 atoms

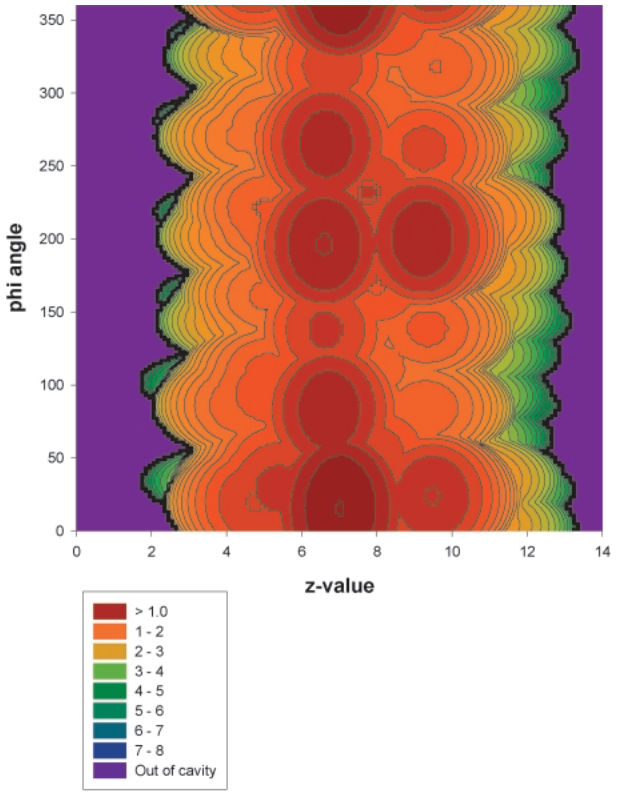

Fig. 4. Cylindrical Coordinates Map of α-CD (ACDHBA) Cavity

The values of ρ (distance from Z-axis to solvent accessible surface of cavity atoms) are shown in the box.

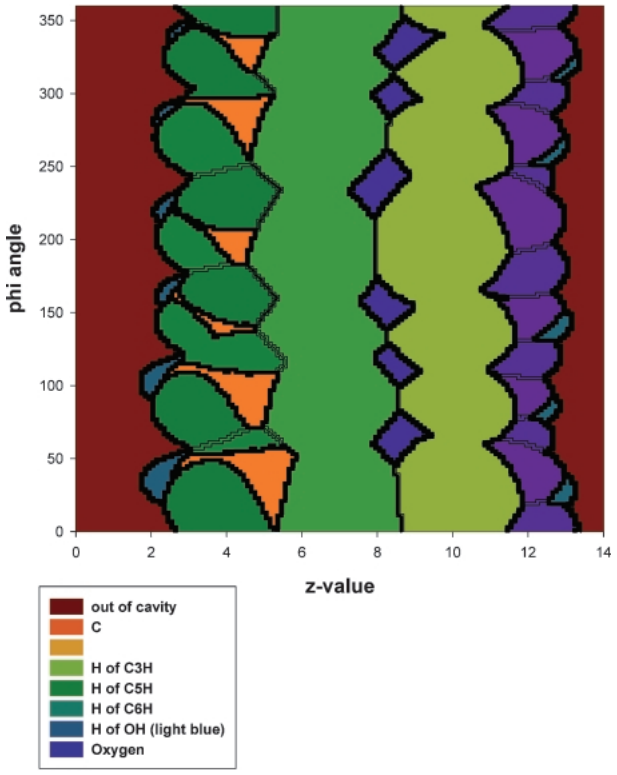

Fig. 5. Surface Character Map of the α-CD Cavity Using the Same Coordinate Set as in Fig. 4

The coloring is shown in the box and described in the text.

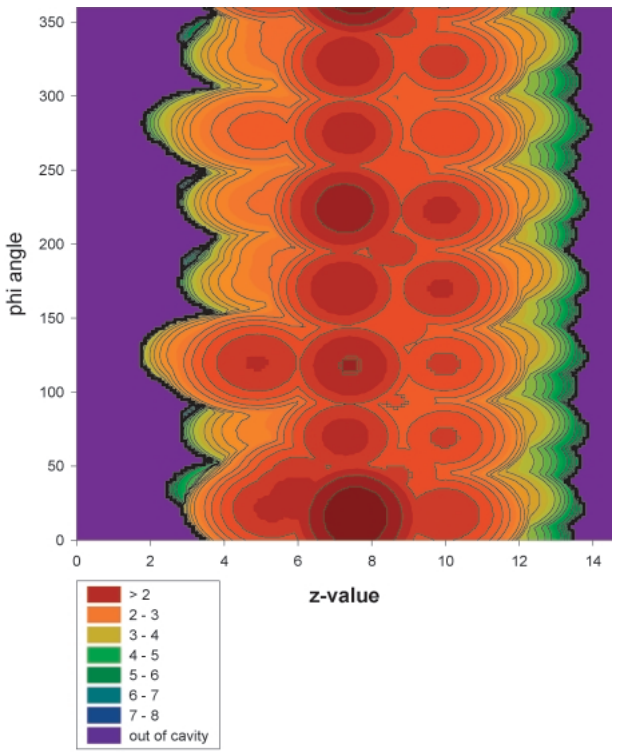

Fig. 6. Cylindrical Coordinate Map of the β-CD (AGAZUD) Cavity Drawn in the Same Manner as in Fig. 4

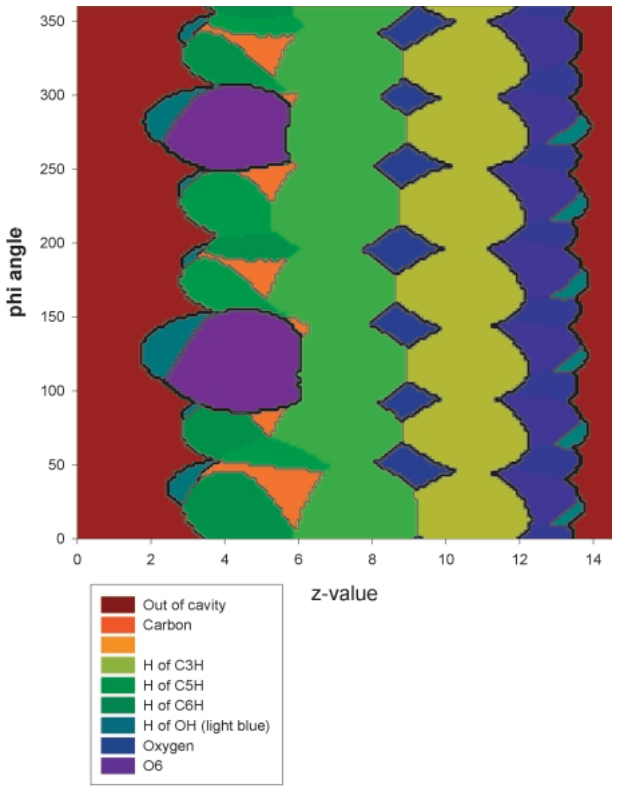

Fig. 7. Surface Character Map of β-CD Cavity Using the Same Coordinate Set as in Fig. 6

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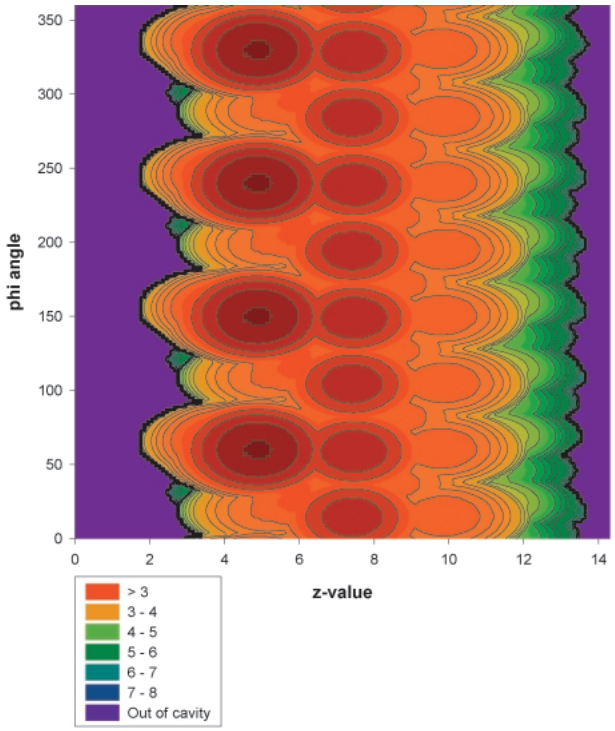


Fig. 8. Cylindrical Coordinate Map of the γ-CD (DOCYID) Cavity Drawn the Same Manner as in Fig. 4

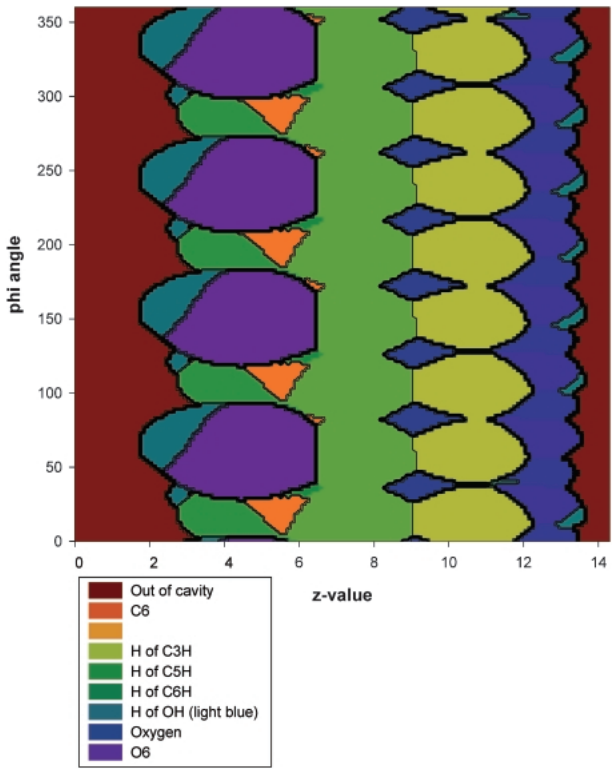


Fig. 9. Surface Character Map of the γ-CD Cavity Using the Same Coordinate Set as in Fig. 8
The coloring is shown in the box and described in the text.

low Z-axis values. The contour of ρ is mapped by changing color with SigmaPlot for Windows 6.00.[20] The O_6 side radius is shorter than that of the O_2 side. In Figs. 10, 11, and 12, the cross-sections with the fixed z-values shown in Figs. 4, 6, and 8 are shown, respectively. ρ changed increasingly as the glucose unit increases from 6 (α-CD) to 8 (γ-CD). Figures 5, 7, and 9 show the surface atomic species of α-, β-, and γ-CD, respectively. The Z-value region from 2.5 to 5.5 Å was occupied by H atoms of C_6–H2 (shown in dark green), C_6 (orange), and sometimes O_6. The H atom of C_5–H occupied the region from 6 Å to 8 Å (green). The region from 9 Å to 11 Å was occupied by the H atom of C_3–H (yellow-green). Around 9 Å, the O_1 area appears (dark blue or purple). In the region of Z-value of more than about 11.5 Å, O_2 and O_3 appeared (purple). H atoms of the O–H group appear on both rims of the cavity (light blue).

As the O_6 is primary alcohol oxygen, it can move around inside and outside of the cavity.[2] Thus, in this study, the positions of O_6 atoms are not always the most stable conformation because they are from crystallographic studies. In Figs. 7 and 9, O_6 atoms appear often but irregularly (purple region with Z-axis value of from 3 Å to 6 Å). Except in low Z-value regions (less than 6 Å), pseudo 6-, 7-, and 8-fold molecular symmetry can be seen and the examples of α- and β-CD shown here have an ellipsoid shape as reported.[7] The maps show that each CD molecule has a rough surface structure with a glucose as one unit around the ϕ-axis of the fixed Z-axis, as shown in Figs. 10, 11, and 12.

The chemical structure and atom positions of the guest molecule of α-, β-, andγ-CD as expressed in the cylindrical coordinate system are shown in Figs. 13, 14, and 15, respectively, together with Fig. 16 which shows the chemical structure of each guest molecule. The common points among these structures are as follows: The hydrophobic part of the guest molecule is positioned at a relatively large Z-axis value (more than 6 Å), that is, they are positioned relatively far from O_6. As it is well known, the guest molecule is mainly surrounded by hydrophobic atomic species,[4,6,7] such as hydrogen atoms of C_5-H and C_3-H[6,7] for which the Z-values are ranged from 6 to 12 Å. The ether oxygen surface area for which the Z-values are from 8 to 9 Å (dark blue or purple) in the guest binding site appears to be relatively small. Some guest atoms in this study are outside the cavity from

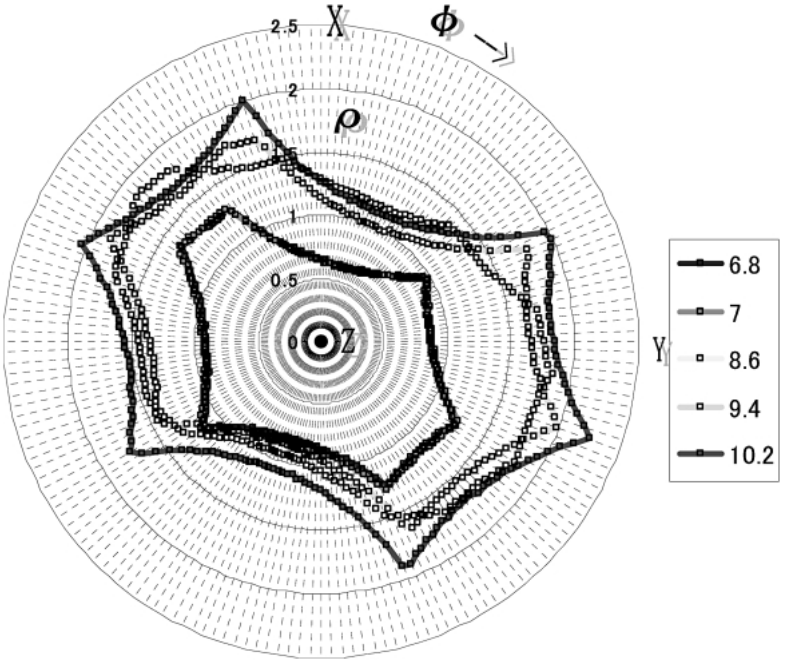


Fig. 10. Cross-section of the α-CD shown in Fig. 4 with Fixed Z-value
Each Z-value is shown in the box for each line graph.

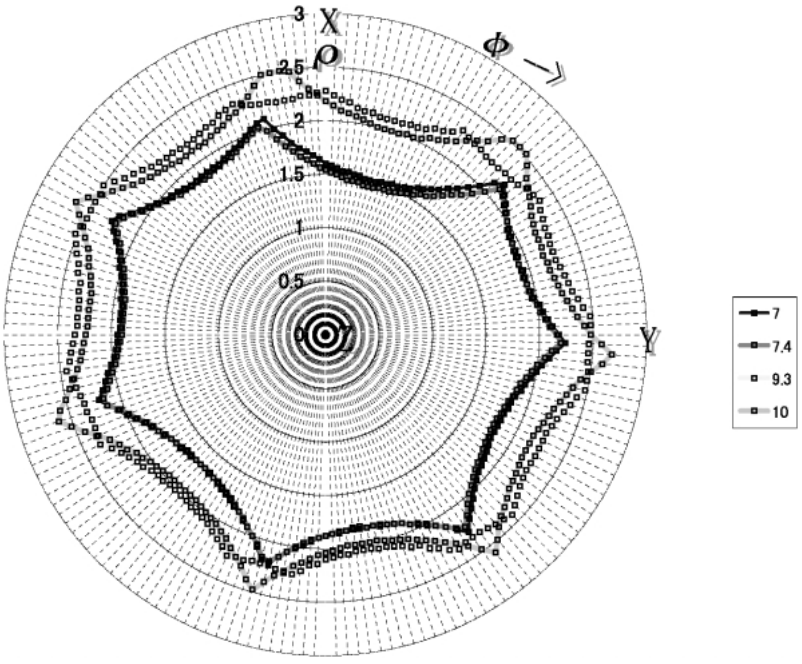


Fig. 11. Cross-section of the β-CD in Fig. 6 with Fixed Z-value
Each Z-value is shown in the box for each line graph.

the wider rim.

In Figs. 13 and 4 (CSD code, ACDHBA,[14] the example of α-CD; the guest, 4-hydroxybezoic acid), the carboxylic acid group is positioned relatively deeply on the narrow rim of CD, and the other end of the benzene group reaches wider rim of CD. The guest molecule runs along the large ρ value part of the cavity to the occupy the longer axis of the principal axis of the ellipsoid of CD. In this case, the O_6 atom of CD does not appear in the map shown in Fig. 4 because crystallographic studies were employed and no water molecule was considered in this study. The H atom of

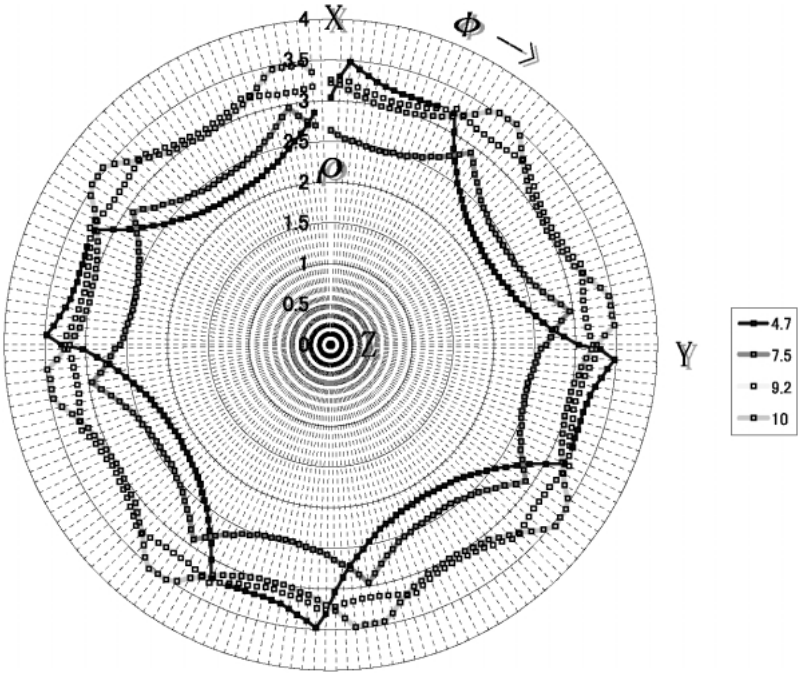


Fig. 12. Cross-section of the γ-CD in Fig. 8 with Fixed Z-value
Each Z-value is shown in the box for each line graph.

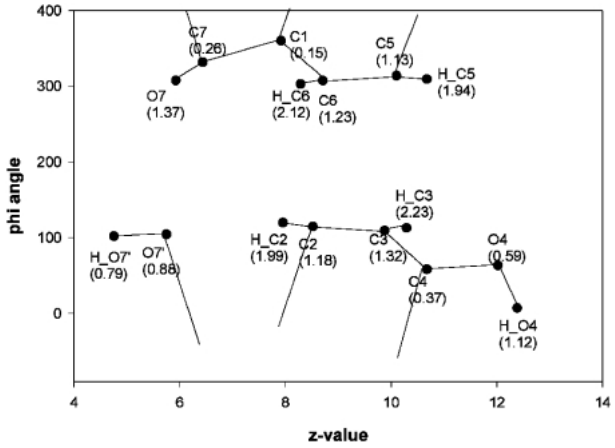


Fig. 13. Molecular Structures of Guest Molecules in α-CD in the Cylindrical Coordinate System
Names of heavy atoms are shown in Fig. 13. Names of the H atom are shown as H_XXx, where XXx denotes bonded heavy atoms, and numerals in parentheses denote radius ρ.

the carboxyl group in this case forms a hydrogen bond with a neighboring CD in the crystal packing,[14] for which the CD packing form is the caged structure.[1]

In Fig. 14 together with Fig. 6 (CSD code, AGAZUD,[15] the example of β-CD; the guest, *N*-acetyl *D*-phenylalanine), as ρ increased more compared to α-CD, the bigger guest molecule can form a complex with β-CD. The carboxylic acid is also positioned relatively deeply to the CD cavity. The carboxyl group in this case forms hydrogen bonds with neighboring water molecules in the crystal packing.[15] The other end of the guest molecule is outside the cavity, that is, the benzene ring of the guest molecule appears to overflow from the cavity. The guest molecule is located along the greater axis of the ellipsoid of the CD cavity, as also shown in the example of α-CD. The crystallographic structure of this complex has two β-CD molecules linked by numerous hydrogen bonds between their secondary hydroxyl group sides to form a head-to-head dimer. One of the two CD molecules and a guest in crystal was adopted to produce Figs. 6, 7, and 14. The part of guest molecule with larger Z-value shown in Fig. 14 reaches the hydrophobic region of the cavity of another CD. The guest molecule on the other CD has a different conformation and occupies a different position from the one shown in Fig. 14. The dimer forms have a channel-type structure packing.[1]

In Fig. 15 together with Fig. 8 (CSD code, DOCYID,[16] the example of γ-CD; the guest, 12-crown-4-ether), ρ increases more than in β-CD. The guest molecule has large ρ width but occupies a narrow Z-value range compared with the guests mentioned in the above two examples, and thus the guest is located in the large Z-value of the CD region and

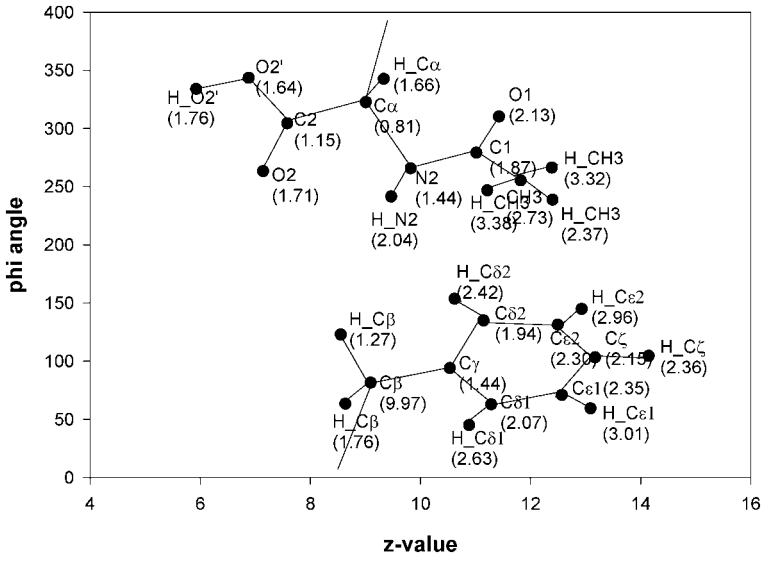


Fig. 14. Molecular Structures of Guest Molecules in β-CD in the Cylindrical Coordinate System
Names of H atoms, numerals in parentheses are similar in manner to those in Fig. 13.

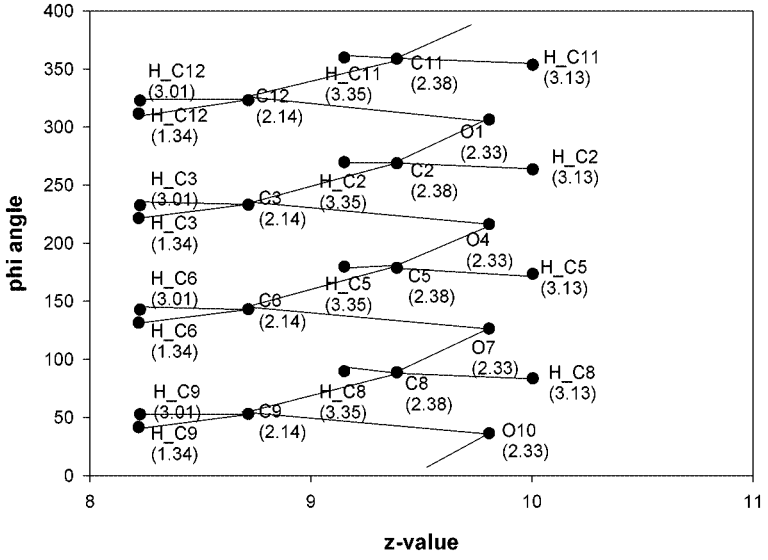


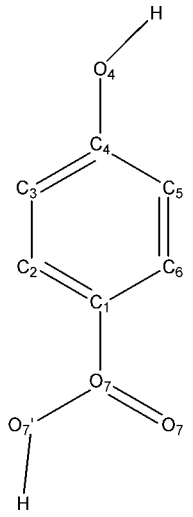
Fig. 15. Molecular Structures of Guest Molecules in γ-CD in the Cylindrical Coordinate System
Names of H atoms, numerals in parentheses are similar in manner to those in Fig. 13.

occupies only the hydrophobic region of CD. As CD and the guest molecule have exact 4-fold symmetry along the Z-axis (crystallographic 4-fold symmetry passing through the center of CD, space group $P42_12$, $Z=6$), almost 8-fold symmetry can be seen, as in shown in Figs. 8 and 12, whereas in the primary alcohol region (Z-value $\sim$5 Å) the CD does not have a circular shape. CDs form the channel-type packing structure in crystal.[1)]

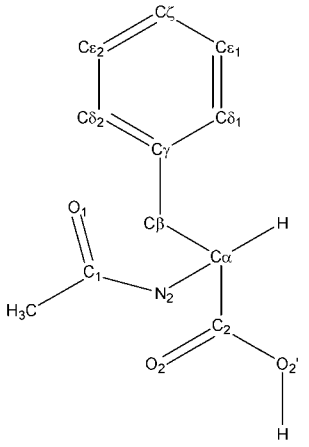
CONCLUSION

It was reported that the guest molecule mainly occupies the hydrophobic region of CD.[4,6,7)] However, mapping in the cylindrical coordinate system was not carried out. Mapping with the cylindrical coordinate system is easy and convenient to obtain information on the inside of a molecule. The method developed here gives not only interaction surface radii, surface roughness, and Z-values but also the characteristics of a molecule which play an important role in the in-

ACDBHA (4-hydroxybenzoic acid)



AGAZUD (N-acetyl-D-phenylalanine)



DOCYID (1,4,7,10-teraoxacyclododecane)

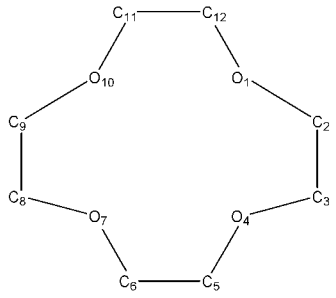


Fig. 16. Chemical Structures and Atomic Names of Guest Molecules to α-, β-, and γ-CD

teraction with a guest molecule. The method can help visualize the hidden part of the molecule clearly. This method also gives the guest position and direction compared with the host cavity in the same coordinate system. By sacrificing observations of the exact chemical structure using 3-dimensional graphics, we can visualize quantitatively the structure and properties on the inside of the host molecule with the help of the guest in the same coordinate system and the considerations mentioned in the Results are easily obtained. This method may be also applicable to the interpretation of an enzyme cavity. And it should be noted that important chemical reactions often occur in the hidden cavity regions in biological molecules.

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